ORIGINAL ARTICLE

Incidence and clinical predictors of endobronchial tuberculosis in patients with pulmonary tuberculosis

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ABSTRACT

Background and objective: **Incidence and predictors of endobronchial tuberculosis (EBTB) remain unknown because of the lack of prospective studies. Our objective was to assess the incidence and predictors of concomitant EBTB in patients with active pulmonary tuberculosis (PTB).**
Methods: **We prospectively performed routine bronchoscopic examination in all patients with PTB to detect EBTB. Clinical and bronchoscopic findings were analyzed to elucidate predictors of EBTB.**
Results: **Bronchoscopies of 429 PTB patients were performed at a tertiary referral hospital in Korea. Among those, 233 patients (54.3%) had EBTB. Female gender (odds ratio (OR) 4.35, 95% confidence interval (CI) 1.78–10.63), longer symptom duration (>4 weeks; OR 1.86, 95% CI 1.05–5.46), and no previous history of tuberculosis (OR 4.16, 95% CI 1.22–14.18) were found to be the independent predictors of concomitant EBTB in patients with active PTB. Most of the EBTB/PTB patients had mild stenosis, and more than 20% of them had severe stenosis at the time of diagnosis. Patients with EBTB had follow-up bronchoscopy to evaluate persistent airway stenosis. Persistent bronchostenosis with the lumen narrowed by more than one third occurred in 20.7% (30/145) of patients. The involvement length and decreased forced expiratory volume in 1 s were the risk factors for persistent bronchostenosis.**
Conclusions: **In patients with active PTB, 50% or more have EBTB. Female gender and longer duration of symptoms are the main predictors of concomitant EBTB. Immediate diagnostic bronchoscopy in patients with active PTB should be considered in selected patients for detection of brocnhostenosis.**

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SUMMARY AT A GLANCE

We performed a prospective study to elucidate incidence and clinical predictors of EBTB. More than 50% of patients with PTB have EBTB. Female gender and longer duration of symptoms are the main predictors of concomitant EBTB.

Key words: bronchoscopy, bronchostenosis, endobronchial tuberculosis, incidence, predictor.

Abbreviations: AFB, acid-fast bacilli; CI, confidence interval; EBTB, endobronchial tuberculosis; FEV1, forced expiratory volume in 1 s; NTM, non-tuberculous mycobacterial; OR, odds ratio; PCR, polymerase chain reaction; PTB, pulmonary tuberculosis.

INTRODUCTION

Endobronchial tuberculosis (EBTB) is defined as a tuberculous infection of the tracheobronchial tree and is the main complication of pulmonary tuberculosis (PTB). EBTB pathogenesis is not yet clear, but may involve direct seeding from parenchymal lesions or bronchial invasion of mediastinal tuberculous lymphadenitis.[1,2]

The reported incidence of EBTB in PTB patients varies greatly (from 6% to 50%).[3–8] Most studies of concomitant EBTB in PTB patients were retrospective, and most results from these studies were obtained for small numbers of patients. The exact incidence of EBTB has not been reported.

To diagnose EBTB, bronchoscopy is the most useful method. Generally, bronchoscopy is selectively performed when EBTB is suspected in patients with severe cough, haemoptysis, wheezing or a positive acid-fast bacilli (AFB) smear with normal chest X-ray. Because EBTB is highly infectious, bronchoscopy may be beneficial, as it allows early detection of EBTB in all patients with active PTB. Even though all patients with PTB may need bronchoscopic examination, bronchoscopy is a somewhat invasive method. There are no exact guidelines or indications to conduct

bronchoscopy for detecting EBTB in patients with PTB. Clinicians need to know the exact incidence of EBTB and patient selection criteria for bronchoscopy among patients with PTB. Identification of EBTB predictors is therefore needed.

We performed this prospective observational study (i) to assess the incidence of EBTB in patients with active PTB and (ii) to identify predictors of EBTB that would be useful for guiding the selection of patients who need bronchoscopy for EBTB detection.

METHODS

Study population

From 2003 to 2005, we prospectively examined by bronchoscopy all patients with newly diagnosed active PTB in a tertiary referral hospital in Daejeon, Korea. We also included patients with relapsed PTB who had been successfully treated more than 1 year ago. Active PTB was defined by a positive AFB smear or positive culture of *Mycobacterium tuberculosis*. The Ziehl-Neelsen stain for sputum smear and both solid and liquid medium for mycobacterial culture were used. Mycobacterial nuclear amplification test (polymerase chain reaction, PCR) was done on some patients if tuberculosis was suspected clinically. Patients with both smear- and culture-negative tuberculosis, drug-resistant PTB, younger than 18 years old, with a positive human immunodeficiency virus test, with malignancy and predicted survival of less than 6 months, with laryngeal tuberculosis or with contraindications to bronchoscopy (such as severe hypoxemia, respiratory failure, recent cardiovascular event or uncontrolled arrhythmia) were excluded.

Patient history, physical examinations, blood tests, chest posterioranterior (PA) X-ray, and sputum examinations were performed at the time of diagnosis and every month during anti-tuberculosis treatment. Simple spirometry was performed at baseline and repeated after completion of the treatment. PTB severity was classified into minimal, moderately advanced and far advanced according to the chest X-ray findings.[6]

Treatment of EBTB was not different with PTB. Anti-tuberculosis treatment was given as a standard 6-month isoniazid, rifampicin, ethambutol and pyrazinamide or 9-month isoniazid, rifampicin, and ethambutol regimen. No additional drugs (such as steroids) for EBTB treatment were given.

The study was approved by the hospital institutional review board. Informed consent was obtained from all patients.

Bronchoscopic examination

Bronchoscopy was performed in all patients with active PTB within 1 week after the initiation of anti-tuberculosis treatment. Bronchial washing or brushing was performed on all visible endobronchial lesions. Bronchoscopic biopsy was performed in the case of differential diagnosis other than tuberculosis. The results of each bronchoscopic examination were reviewed and classified by two pulmonary specialists.

EBTB was defined by the presence of a visible endobronchial lesion proximal to a segmental bronchus, with a histological proof from bronchial biopsy or positive smear of the bronchial washing or brushing fluid. EBTB was classified into seven subtypes by using the Chung's method: actively caseating, fibrostenotic, oedematous-hyperaemic, tumorous, ulcerative, granular, and the non-specific bronchitic type.[3]

If a patient had two or more subtypes of EBTB simultaneously, EBTB was classified by the dominant form. We also classified EBTB by the number of involved levels. Single-level EBTB was defined when only one site of trachea, main bronchus or lobar bronchus was involved. EBTB that involved two or more bronchial levels was defined as multiple-level EBTB. For example, EBTB in trachea only was classified as single-level EBTB. EBTB that involved one main bronchus and one lobar bronchus was classified as multiple-level EBTB. EBTB that occurred proximal to the lobar bronchi was defined as central EBTB. This type has a potential to develop symptomatic stenosis. We also measured the length of the endobronchial involvement of tuberculosis by guidance of forceps.

The endobronchial narrowing was measured by comparing the area and graded as follows:
Grade 1, luminal narrowing <one third;
Grade 2, luminal narrowing ≥one third but <two thirds;
Grade 3, luminal narrowing ≥two thirds.

In case of multiple-level EBTB, the length was shown as the sum of each involvement, and the worst narrowing level among the central involvements was graded as luminal narrowing.

Follow-up bronchoscopy was planned in patients with central EBTB after at least 4 months of anti-tuberculosis chemotherapy to evaluate bronchostenosis as a late complication of EBTB and to determine whether the initial routine bronchoscopy was needed.
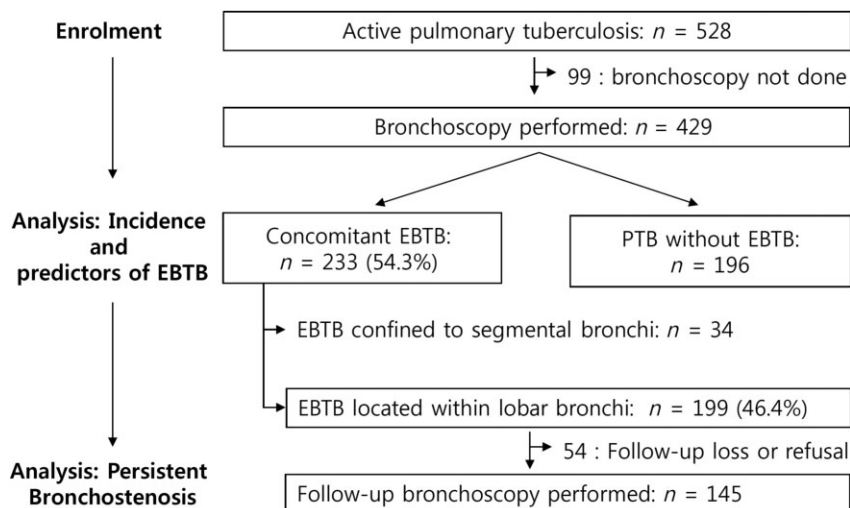
Statistical analysis

Statistical analysis was carried out with SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA). To search for associations between clinical characteristics and concomitant EBTB, we used logistic regression analysis. A χ^2 test was used to compare the differences between categorical patient characteristics. *P* values < 0.05 were considered significant.

RESULTS

Incidence of EBTB and bronchoscopic findings

In total, 528 patients with newly diagnosed active PTB were observed during the study period. Among them, 99 patients refused bronchoscopy or bronchoscopy was not suitable because of hypoxemia or respiratory failure. Routine bronchoscopy was performed for evaluation of concomitant EBTB in 429 patients (247 males, 182 females) within 3 days after initiation of anti-tuberculosis treatment, and EBTB was diagnosed in 233 (54.3%). A total of 122 (28.4%) patients were

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Enrolment        ┌─────────────────────────────────────────────┐
                 │ Active pulmonary tuberculosis: n = 528      │
                 └─────────────────────────────────────────────┘
                              ↓→ 99 : bronchoscopy not done
                 ┌─────────────────────────────────────────────┐
                 │ Bronchoscopy performed: n = 429             │
                 └─────────────────────────────────────────────┘
Analysis: Incidence    ┌──────────────────┐      ┌──────────────────┐
and                    │ Concomitant EBTB:│      │ PTB without EBTB:│
predictors of EBTB     │ n = 233 (54.3%)  │      │ n = 196          │
                       └──────────────────┘      └──────────────────┘

                 → EBTB confined to segmental bronchi: n = 34

                 → EBTB located within lobar bronchi: n = 199 (46.4%)
                              ↓→ 54 : Follow-up loss or refusal
Analysis: Persistent
Bronchostenosis    Follow-up bronchoscopy performed: n = 145
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Figure 1 Flow chart of the routine observational bronchoscopy in patients with pulmonary tuberculosis: a total of 528 patients were diagnosed as active pulmonary tuberculosis. Among them, 429 patients were enrolled, and bronchoscopy was performed. EBTB, endobronchial tuberculosis.

Table 1 Incidence of EBTB in patients with PTB

	%
Overall incidence	54.3 (233/429)
Incidence by gender	
Males (*n* = 247)	43.3 (107/247)
Females (*n* = 182)	69.2 (126/182)
Incidence by location	
Located within lobar bronchi	46.4 (199/429)
Confined to segmental bronchi	7.9 (34/429)
Incidence by subtypes	
Actively caseating	26.6 (114/429)
Others	27.7 (119/429)

EBTB, endobronchial tuberculosis; PTB, pulmonary tuberculosis.

Table 2 Characteristics of EBTB according to bronchoscopic features

Bronchoscopic features	*n* (%)
Type of EBTB	
Actively caseating	114 (48.9)
Oedema or hyperaemia	87 (37.3)
Other types[†]	32 (12.8)
Length of involvement (mm) (±SD)	24.31 (±21.8)
Site involved	
Central airways	199 (85.4)
Trachea	38 (16.3)
Main bronchi	58 (24.9)
Lobar bronchi	103 (44.2)
Segmental bronchi	34 (14.6)
Levels involved	
Single	152 (65.2)
Multiple	81 (34.8)
Stenosis grade (central EBTB; *n* = 199)	
Grade 1	140 (70.4)
Grade 2 or 3	59 (29.6)
Grade 2	30 (15.1)
Grade 3	29 (14.5)

[†] Including 11 patients with fibrostenotic, 2 tumorous, 3 ulcerative, 4 granular, and 12 non-specific bronchitic type.

EBTB, endobronchial tuberculosis; SD, standard deviation.

biopsy-proven EBTB cases; others were diagnosed by positive bronchial washing. Among these, more clinically significant central EBTB was diagnosed in 199 (46.4%) patients. Highly infectious actively caseating EBTB was diagnosed in 114 (26.6%) patients. The incidence of EBTB was 43.3% in males and 69.2% in females. The flow chart of the study is shown in Figure 1; the results on the incidence of EBTB are summarized in Table 1.

Table 2 shows the overall bronchoscopic findings. Actively caseating EBTB was found to be the main type (48.9%, 114/233). Lobar bronchi were the most common site of endobronchial involvement (44.2%, 103/233). The mean length of involvement exceeded 20 mm. In most patients, the level of EBTB was single, but 35% of patients had multiple-level EBTB. Among patients with central EBTB, 14.5% had grade 3 bronchostenosis at the time of diagnosis.

Characteristics of the patients

The baseline clinical characteristics of the 429 patients are summarized in Table 3. Most of patients were smear and culture positive. A total of 27 patients with only smear positive were diagnosed by PCR positive. The median age of patients was 48 years (range 18–97 years). Approximately 20% (88/429) of patients had an underlying disease associated with the increased risk of tuberculosis. Diabetes was most common underlying disease, followed by alcoholism and chronic liver disease.

The main symptom was cough (53.7%). In asymptomatic patients (26 patients or 7.2%), active PTB was diagnosed due to an abnormality detected by regular chest X-ray examination. The average time from PTB symptoms to diagnosis was 7.5 weeks (range, 0–52 weeks). Symptom duration was <4 weeks in 44.7% (192/429) and >4 weeks in 55.3% (237/429).

Table 3 Clinical characteristics of 429 patients with PTB examined by bronchoscopy

Characteristics	Overall (*n* = 429)	EBTB(+) (*n* = 233)	EBTB(−) (*n* = 196)	*P*-value
Age (years), Median (range)	48 (18–97)	47 (18–97)	48 (18–84)	0.930
Sputum AFB				
Smear positive	366	232	134	<0.001
Culture positive	402	227	175	<0.001
Both smear and culture positive	339	226	113	
Gender				
Male (%)	247 (57.6)	107 (45.9)	140 (71.4)	<0.001
Female (%)	182 (42.4)	126 (54.1)	56 (28.6)	
Main symptoms				<0.001
Cough (%)	195 (53.7)	124 (62.3)	71 (43.3)	
Non-cough (%)	142 (39.1)	62 (31.2)	80 (48.8)	
Asymptomatic (%)	26 (7.2)	13 (6.5)	13 (7.9)	
Symptom duration				
Mean (range, weeks)	7.5 (0–52)	8.25 (0–52)	6.19 (0–48)	0.083
Duration				
<4 weeks (%)	192 (44.7)	67 (30.9)	94 (51.9)	<0.001
≥4 weeks (%)	237 (55.3)	150 (69.1)	87 (48.1)	
Previous history of PTB				0.002
Yes (%)	77 (17.9)	29 (12.7)	47 (24.1)	
No (%)	352 (82.1)	199 (87.3)	148 (75.9)	
Co-morbid disease				0.003
Absent (%)	341 (79.5)	198 (85.0)	143 (73.0)	
Present (%)	88 (20.5)	35 (15.0)	53 (27.0)	
Severity by CXR				
Minimal (%)	152 (47.8)	84 (47.7)	68 (47.9)	0.995
Moderate advanced (%)	116 (36.5)	64 (36.4)	52 (36.6)	
Far advanced (%)	50 (15.7)	28 (15.9)	22 (15.5)	
CXR finding				
No cavitary disease (%)	253 (79.6)	138 (78.5)	115 (81.0)	0.614
Cavitary disease (%)	65 (20.4)	38 (21.5)	27 (19.0)	
No atelectasis (%)	192 (74.7)	98 (70.0)	94 (80.3)	0.164
Atelectasis (%)	65 (25.3)	42 (30.0)	23 (19.7)	
Initial FEV1 (% predicted)	89.2 ± 22.3	88.3 ± 22.4	91.1 ± 21.8	0.226

PTB, pulmonary tuberculosis; EBTB, endobronchial tuberculosis; CXR, chest X-ray; FEV1, forced expiratory volume in 1 s.

Some patients (17.9%) had a history of PTB diagnosed by history of complete anti-tuberculosis treatment more than 1 year before the study, but most of patients (82.1%) had no previous history of PTB. PTB severity revealed by chest X-ray was as follows: minimal disease was found in 47.8% of the patients, moderately advanced in 36.5% and far advanced in 15.7%. According to chest X-ray, only 20.4% patients had cavities, and 25.3% had atelectasis. Simple spirometry was almost normal in all patients: mean forced expiratory volume in 1 s (FEV1) was 2.56 L (89% of the predicted normal value).

To elucidate the predictors of EBTB, we compared the clinical parameters (sex, underlying diseases, symptoms, symptom duration, pulmonary function test and chest X-ray findings) between EBTB-positive and EBTB-negative PTB patients. Age was not significantly different between the two groups. EBTB was more frequent in females than in males ($P < 0.001$). Patients with cough as the main complaint had higher incidence of EBTB than patients with non-cough symptoms ($P = 0.001$). Patients without past history of

tuberculosis also had a significantly higher incidence of concomitant EBTB than patients with a previous history of tuberculosis ($P = 0.002$). Other parameters, such as simple spirometry test, severity of PTB by chest X-ray, and the presence or absence of cavity or atelectasis were similar in patients with and without EBTB. EBTB was more frequent in patients with longer symptom duration (>4 weeks; $P < 0.001$) (Table 3).

Predictors of EBTB

Univariate logistic regression analysis revealed that female gender, symptoms with cough, no previous history of PTB, co-morbid disease and symptom duration of more than 4 weeks were significant predictors of concomitant EBTB. However, multivariate regression analysis confirmed only female gender (odds ratio (OR) = 4.35, 95% confidence interval (CI): 1.78–10.63), symptom duration of more than 4 weeks (OR = 1.86, 95% CI: 1.05–5.46), and no previous history of PTB (OR = 4.16, 95% CI: 1.22–14.18) as the significant predictors of concomitant EBTB (Table 4).

Table 4 Predictors of concomitant EBTB

	Univariate			Multivariate[†]		
Variables	Odds ratio	95% Confidence interval	*P*-value	Odds ratio	95% Confidence interval	*P*-value
Age, ≥50 years old	1.00	0.99–1.01	0.954	1.24	0.52–2.93	0.632
Sex, female	3.02	2.02–4.52	0.000	4.35	1.78–10.63	0.001
Cough, present	2.17	1.42–3.30	0.000	1.50	0.34–2.00	0.660
Symptom duration, ≥4 weeks	2.42	1.61–3.64	0.000	1.86	1.05–5.46	0.049
Previous history, none	2.18	1.31–3.63	0.003	4.16	1.22–14.18	0.023
Co-morbid disease, absent	2.10	1.30–3.38	0.002	2.15	0.73–6.36	0.168
Atelectasis on CXR, present	1.79	1.00–3.20	0.048	1.24	0.14–1.17	0.093
Cavity on CXR, present	1.17	0.68–2.04	0.571	1.26	0.39–4.06	0.695
Severity by CXR, moderate or far advanced	1.01	0.65–1.57	0.977	1.15	0.54–2.42	0.718
Initial FEV1, <80% of the predicted value	1.46	0.73–2.95	0.289	1.731	0.65–4.59	0.269

[†] Adjusted by all other variables in the table.
EBTB, endobronchial tuberculosis; CXR, chest X-ray; FEV1, forced expiratory volume in 1 s.

Table 5 Comparison of EBTB by sex according to bronchoscopic features

Bronchoscopic features	Overall (n = 233)	Males (n = 107)	Females (n = 126)	*P*-value
Type of EBTB				
Actively caseating (%)	114 (48.9)	37 (35.2)	77 (62.6)	0.003
Other types (%)	119 (51.1)	68 (64.8)	46 (37.4)	
Length of involvement (mm) (±SD)	24.31 (±21.8)	19.05 (±16.5)	29.19 (±25.0)	0.485
Central airway involvement	199 (85.4)	89 (83.2)	110 (87.3)	0.360
Trachea (%)	38 (16.3)	16 (15.0)	22 (17.5)	
Main bronchi (%)	58 (24.9)	21 (19.6)	37 (29.4)	
Lobar bronchi (%)	103 (44.2)	52 (48.6)	51 (40.4)	
Level of involvement				
Single (%)	151 (65.0)	75 (70.7)	76 (60.3)	0.097
Multiple (%)	81 (35.0)	31 (29.3)	50 (39.7)	
Stenosis grade in central EBTB				
Grade 1 (%)	138 (70.1)	69 (79.3)	69 (62.7)	0.009
Grade 2 or 3 (%)	59 (29.9)	18 (20.7)	41 (37.3)	

EBTB, endobronchial tuberculosis; SD, standard deviation.

We analyzed clinical and bronchoscopic characteristics of all 233 patients with EBTB by gender. Clinical characteristics such as median age, symptoms and their duration, and a previous history of PTB were not different by gender. Fewer female than male patients with EBTB had underlying diseases or risks for PTB (*P* = 0.001) (data not shown).

The differences in bronchoscopic findings by gender are shown in Table 5. Female patients had a higher incidence of actively caseating EBTB (*P* = 0.003). Bronchostenosis of grade 2 or 3 was more frequent in females (37.3%) than in males (20.7%; *P* = 0.009). The frequencies of central EBTB and multiple levels of involvement were higher in female patients, but the difference did not reach statistical significance.

Endobronchial stenosis after treatment

Table 6 shows follow-up bronchoscopic results on late bronchostenosis. Most EBTB patients improved

following standard anti-tuberculosis therapy without steroids. However, grade 2 or 3 bronchostenosis developed in some patients (20.7%, 30/145). We analyzed the risk factors for persistent grade 2 or 3 bronchostenosis. In univariate analysis, female gender, decreased FEV1 and the involvement length of >20 mm were the risk factors for persistent stenosis. Yet, multivariate analysis confirmed only the involvement length, and decreased FEV1 as the risk factors for persistent stenosis (Table 7).

As a result, three patients underwent bronchoscopic interventions (one balloon dilatation only, two stent insertion after balloon dilatation). All these three patients were women and had stenosis in the left main bronchus.

DISCUSSION

To the best of our knowledge, this is the first report of a prospective study of the incidence and predictors of

Table 6 Bronchostenosis in patients with central EBTB after standard anti-tuberculosis therapy

		Persistent bronchostenosis after treatment		
		Grade 1 (%)	Grade 2 or 3 (%)	*P*-value
Initial luminal narrowing in central EBTB	Grade 1 (*n* = 106)	86 (81.1)	20 (18.9)	0.450
	Grade 2 (*n* = 19)	13 (68.4)	6 (31.6)	
	Grade 3 (*n* = 20)	16 (80.0)	4 (20.0)	
Total		145	115 (79.3)	30 (20.7)

EBTB, endobronchial tuberculosis.

Table 7 Risk factors for grade 2 or 3 stenosis after treatment

	Univariate			Multivariate[†]		
Variables	Odds ratio	95% Confidence interval	*P*-value	Odds ratio	95% Confidence interval	*P*-value
Age, ≥50 years old	0.99	0.96–1.02	0.570	0.79	0.28–22.68	0.891
Sex, female	2.34	1.01–5.40	0.047	2.66	0.72–98.41	0.595
Cough, present	1.50	0.63–3.59	0.364	1.82	0.03–105.83	0.774
Symptom duration, ≥4 weeks	0.73	0.34–1.87	0.601	2.63	0.17–40.88	0.490
Previous history of PTB, none	1.57	0.44–5.67	0.491	10.89	0.01–951.32	0.490
Atelectasis on CXR, present	2.65	0.86–8.21	0.091	5.57	0.02–189.73	0.564
Cavity on CXR, present	0.80	0.27–2.84	0.687	3.51	0.05–264.10	0.569
Severity by CXR, moderate or far advanced	1.17	0.47–9.28	0.742	1.05	0.02–63.90	0.359
Initial FEV1, <80% of the predicted value	6.98	1.74–28.07	0.006	4.97	1.01–23.06	0.041
Length of involvement, ≥20 mm	5.68	2.22–14.83	0.000	16.33	1.90–141.10	0.011
Type of EBTB, actively caseating	1.94	0.87–4.33	0.107	4.32	0.10–179.51	0.442
Level of involvement, multiple	2.15	0.99–4.64	0.052	20.60	0.24–181.30	0.185
Initial stenosis, grade 2 or 3	1.33	0.56–3.14	0.518	0.14	0.00–66.40	0.243

[†] Adjusted by all other variables in the table.
EBTB, endobronchial tuberculosis; PTB, pulmonary tuberculosis; CXR, chest X-ray; FEV1, forced expiratory volume in 1 s.

EBTB, whereas the data available so far were provided only by retrospective studies or pre-fibre-optic bronchoscopic reports. By using prospective routine bronchoscopy in 429 patients with PTB, we found that the incidence of EBTB was 54.3%. The data from autopsy of patients with active PTB showed that the frequency of EBTB was 30–50%.[9–11] Despite the higher incidence of EBTB suggested by these autopsy data, the frequency of EBTB was generally known to be about 10%.[12] Our estimate is consistent with the previous autopsy studies[9–11] and is higher than the estimates from other retrospective studies.[9–12]

High incidence of EBTB raises questions related to clinical applications. One question is whether bronchoscopic examination should be performed in every patient with active PTB. The other question is what the risk factors are for EBTB in patients with PTB. Our results show that female patients with longer symptom duration (>4 weeks) or no previous history of PTB need bronchoscopic examination for detection of concomitant EBTB.

Our findings are in line with some retrospective studies that also showed that female gender was associated with concomitant EBTB.[12–16] But there have been no prospective studies demonstrating the female gender as a risk factor for EBTB in patients with PTB. Our study is the first to show that female gender is the main risk factor for concomitant EBTB.

Why is concomitant EBTB more likely in female patients? Some possible causes have been proposed. One may be a longer exposure to tubercle bacilli, because female patients have less expectorated sputum containing bacilli due to sociocultural and aesthetic factors.[6] Rikimaru *et al.* postulated that a structural difference may play a role. Female bronchi are narrower than those of males, which may make females more susceptible to EBTB.[17] Smoking may also be related to concomitant EBTB. Frequent smokers are less likely to develop EBTB, so in females, who are more likely to smoke less, EBTB arises more frequently.[17] Our study was not designed in a way to allow us to elucidate the reasons for higher frequency of EBTB in females. Female gender was also a risk factor for a higher grade of stenosis, and females had a more active type of EBTB and a tendency to have multiple-level EBTB. Further observational studies are needed to define the differences between females and males in this respect.

Symptom duration is also presumed to be a risk factor of concomitant EBTB. A previous retrospective study showed that longer symptom duration was associated with a higher frequency of EBTB.[18] In the

present study, longer symptom duration (>4 weeks) was an independent risk factor for EBTB in patients with PTB. We believe that longer symptom duration may be related to a longer exposure to tubercle bacilli and thus contributes to EBTB development. We expected that longer symptom duration would also be related to the levels of involvement and to the grade of stenosis, but our study did not confirm this relation for symptom duration. More data about the grade of stenosis are required to perform this analysis properly.

Sakin *et al.* found that EBTB was more common in patients with advanced cavitary tuberculosis.[19] In cavitary tuberculosis, more tubercle bacilli are usually dispersed, and longer exposure to bacilli on the airway increases the chance of bronchial spread. Thus, patients with cavitary tuberculosis may be more frequently affected by EBTB. However, our study did not show the relationship between cavitary tuberculosis or advanced tuberculosis and concomitant EBTB. A possible explanation of this result could be that although patients with cavitary tuberculosis had numerous bacilli, the release of these bacilli was less pronounced than expected.

In the present study, the incidence of EBTB differed according to the previous history of tuberculosis: EBTB was more frequent in the initial treatment group than in the retreatment group. We do not know why patients without history of treatment were more at risk of having EBTB. In univariate analysis, atelectasis was related to concomitant EBTB, but in multivariate analysis, it was not a risk factor. Atelectasis was only found in 15% of EBTB cases. Some studies claimed that young age was a risk factor for EBTB.[20] However, our study did not find any differences in concomitant EBTB frequencies by age group. In summary, we found female gender, longer symptom duration (>4 weeks) and the initial treatment to be the independent clinical predictors for concomitant EBTB in patients with PTB.

High incidence of EBTB may be relevant for clinical practice. Routine bronchoscopy may be needed for female patients or patients with longer symptom duration. However, follow-up bronchoscopy did not show the effectiveness of early diagnostic bronchoscopy in terms of active identification and prevention of persistent bronchostenosis. Most patients with EBTB improved after standard anti-tuberculosis therapy. Female gender was not a risk factor for persistent bronchostenosis. Thus, the risk factors for EBTB and persistent bronchostenosis are different. Bronchoscopic finding (the involvement length of >20 mm) was the only risk factor for grade 2 or 3 persistent bronchostenosis. In a previous retrospective study based on only follow-up bronchoscopy performed only in patients with severe EBTB, fibrostenotic type is identified as one of the predictor of persistent bronchostenosis.[4] But in our study based on all patients with EBTB, type of EBTB was not the predictor of bronchostenosis.

The present study has several limitations. First, some patients enrolled in this study could have had non-tuberculous mycobacterial (NTM) infection as we did not perform nuclear amplification test (PCR) in all patients. Up to 10% of patients with positive AFB stain may actually be suffering from NTM pulmonary disease in Korea.[21] But endobronchial lesions as a result of NTM are extremely rare. Just a few cases were reported.[22] So high incidence of EBTB would not have been affected by the eventual presence of NTM cases. Second, we did not consider the sputum AFB grade as a variable for risk factor analysis because the method of sputum collection, such as timing, was not controlled. Other possible risk factors such as smoking or alcohol drinking history were not analyzed. Third, about half of the patients with EBTB were diagnosed by bronchial biopsy, and other patients diagnosed by bronchial washing only. Some patients might thus have showed false positive EBTB results, especially in non-caseating types.

The importance of this study is that it has prospectively revealed the incidence and the predictors of EBTB in patients with active PTB, and also the risk factors for persistent bronchostenosis after treatment. The incidence of EBTB in patients with active PTB was at least 50% and was strikingly higher than that reported by previous retrospective studies. Female gender and longer symptom duration were the main independent predictors of concomitant EBTB. Bronchoscopy revealed length of involvement as an independent risk factor for persistent bronchostenosis. Thus, our findings suggest that females and patients with longer symptom duration should be considered for bronchoscopy to detect endobronchial involvement. But in terms of bronchostenosis after treatment, recommendation for immediate diagnostic bronchoscopy in patients with active PTB should be considered in selected patients.

Acknowledgements

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